REMARKS/ARGUMENTS

Amendments:

Claims 1-13 and 33 are pending. Claim 1 was amended to incorporate the recitations of claims 3, 4, 5, and 8. Support for the amendment to claim 1 is in original claims 1, 3, 4, 5 and 8.

Claims 3-5, 7-8 and 11-12 are canceled.

Claim 6 has been amended to depend on claim 2 - to correct a typographical error.

Claim 9 has been amended to depend on claim 1 instead of canceled claim 8.

Claim 10 has been amended to recite that the cooked composition is prepared according to the method of claim 1. Support for this amendment is in original claims 1 and 10.

Claim 33 has been added to more clearly define the invention. Support for the new claim is in original claims 1, 3, 4, 5, and 8. Further, claim 33 has been added to correct a typographical error in numbering.

No new matter is added and the entry of the amendments is respectfully requested.

Claim Objections

The claims were objected to because two claims were mistakenly listed as claim 22. Applicants have canceled claims 12-32 to remove this inconsistency. Claim 33, erroneously listed as claim 32, has been amended to correct the typographical error. Since the pending claims, as amended, no longer contain duplicate numbers, withdrawal of this objection is respectfully requested.

Specification Objections:

The Examiner has objected to the specification as allegedly containing improper incorporations by reference (Office Action, page 2). The Examiner states that the instant application uses "omnibus" language and fails to teach with particularity where specific

information is to be found in each reference. *Id.* In support of this objection, the Examiner cited *Advanced Display Systems, Inc. v. Kent State Univ.*, 54 U.S.P.Q.2d 1673 (Fed. Cir. 2000) and also highlighted sections of *Advanced Display Systems, Inc.* that cited *In re Seversky*, 474 F.2d 671 (C.C.P.A. 1973) and *In re Lund*, 376 F.2d 982 (C.C.P.A. 1967). Applicants respectfully traverse this objection.

First, the *Seversky* and *Lund* cases are not applicable to the instant application. In the *Seversky* case, the Court of Customs and Patent Appeals held that the simple statement that a daughter application was a "continuation-in-part" of a parent application was insufficient to incorporate the parent application by reference. *Seversky*, 474 F.2d at 674. In the *Lund* case, the Court of Customs and Patent Appeals held that a single sentence in a pending application indicating that it was a "continuation-in-part" of an abandoned application was insufficient to incorporate the abandoned application by reference. *Lund*, 376 F.2d at 989. By contrast, the instant application contains clear language that the cited publications are "incorporated by reference" in the application. *See, inter alia*, page 10, lines 1-2 and page 28 last paragraph of the specification. Thus, *Seversky* and *Lund* are irrelevant to the instant case.

Second, Applicants have specifically described where the information is found in the incorporated references. According to *Advanced Display Systems*, the incorporated material must be described with sufficient particularity to "one reasonably skilled in the art." *Advanced Display Systems*, 54 U.S.P.Q.2d at 1680. The instant specification discloses the first author, journal, volume, year, and page numbers for the incorporated publications. As an example, the paragraph spanning pages 4, lines 19-24 of the specification states:

> FISH has historically been combined with classical staining methodologies in an attempt to correlate genetic abnormalities with cellular morphology [see e.g., Anastasi et al., Blood 77:2456-2462 (1991); Anastasi et al., Blood 79:1796-1801 (1992); Anastasi et al., Blood 81:1580-1585 (1993); van Lom et al., Blood 82:884-888 (1992); Wolman et al., Diagnostic Molecular Pathology 1(3): 192-199 (1992); Zitzelberger, Journal of Pathology 172:325-335 (1994)]. However, several of these studies address hematological disorders where genetic changes

> are assessed in freshly fixed smears from bone marrow aspirates or peripheral blood specimens. United States Patent No. 6,573,043 describes combining morphological staining and/or immunohistochemistry (IHC) with fluorescence in situ hybridization (FISH) within the same section of a tissue sample.

Thus, the instant application discloses the first author, journal, volume, year, and page numbers for the Anastasi publications (6 pages each) and the van Lom (5 pages), Wolman (8 pages), and Zitzelberger publications (11 pages). It is respectfully asserted that one of skill in the art would know where to find these publications, and would be able to read the very small number of pages contained therein. Rather than "omnibus" language, the instant application uses specific citations that are accessible to skilled persons in the art.

Third, Applicants point to the level of particularity that is required by the courts. In *National Latex Products*, the Sixth Circuit held that a brief statement was sufficient for incorporation by reference: "A suitable apparatus for continuous internal casting is shown in the application of Henry Martin and Paul Rekettye, Serial No. 179,726 filed August 16, 1950..." *National Latex Products*, 274 F.2d at 230; U.S. Pat. No. 2,629,134, col. 4. In *In re Fried*, The Court of Customs and Patent Appeals held that a short statement was sufficient for incorporation by reference: "The...steroid reactants can be prepared as disclosed in the applications of Josef Fried, Serial Nos. 489,769 and 515,917, filed February 21, 1955, and June 24, 1955, respectively." *In re Fried*, 329 F.2d 323, 325 (C.C.P.A. 1964). Compared to these statements of incorporation, Applicants have certainly provided sufficient particularity.

For all of these reasons, Applicants respectfully assert that the specification includes proper incorporations by reference. Withdrawal of this objection is respectfully requested.

§ 112 First Paragraph - written description

Claims 1-13 and 33 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement (Office Action, page 5). The Examiner states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the Inventors

had possession of the claimed invention and raised a number of issues to support the rejection. *Id.* Each one of these issues is addressed below.

First, the Examiner states that the claimed method encompasses the preparation of fixed material from cells or tissue derived from any plant, as well as from any tissue found in any mammal, and therefore lacks sufficient written description (Office Action, page 8). For this rejection, the Examiner relies on the court's decision in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1405 (Fed. Cir. 1997) (See, Office Action, sentence spanning pages 7 and 8). Applicants respectfully traverse as follows.

University of California is clearly distinguished from the instant case. In *University of California*, the claims at issue were directed to recombinant plasmid with an insert that encodes insulin. *University of California*, 43 U.S.P.Q.2d at 1401. The Court held that the claims required human insulin-encoding cDNA and such cDNA was not disclosed in the specification. *University of California*, 43 U.S.P.Q.2d at 1404-05. Because of this, the Court affirmed a lower court decision that the claims are invalid. Id. at 1405.

In contrast to the University of California case, Applicants' claimed invention is directed to methods of preparing tissues for *in situ* hybridization after the tissues samples have been prepared (See, e.g., claim 2 of the instant Application). In some instances, the prepared tissue is already fix treated (See, e.g., claim 1 of the instant Application). Therefore, the focus on the written description for such methods is misplaced. Applicants traverse this rejection because the claims are not directed to methods of preparing tissue samples or fixing tissue. See, e.g., independent claims 1, 10 and 32. Methods of preparing tissues from various cell types, including methods for preparing fix treated tissue, are not claimed by the pending claims. Since preparation of tissues and fixed treated tissue is not claimed, it is immaterial whether the instant specification provide adequate description of how to prepare tissues from various cell types.

Furthermore, the preparation of fixed treated tissue is well known at the time the instant application was filed (i.e., November 20, 2002). For example, methods for fixing various tissues are listed in *Manual of Histological Staining Method of the Armed Forces Institute of Pathology*

(3rd edition (1960) Lee G. Luna, HT (ASCP) Editor, The Blakston Division McGraw-Hill Book Company, New York (Exhibit 1)) and in the *Armed Forces Institute of Pathology Advanced Laboratory Methods in Histology and Pathology* (1994) Ulreka V. Mikel, Editor; Armed Forces Institute of Pathology, American Registry of Pathology, Washington, D.C. (Exhibit 2)).

In fact, methods of preparing fixed tissue was sufficiently advanced by the time the instant Application was filed that automated tissue fixing machines were commonly patented. Automated tissue fixing technology are claimed in numerous issued US patents including, at least, US 6,058,788 (automated machine for fixing tissues (Exhibit 3)), US 4,834,943 (tissue processor for fixing and embedding resin impregnated specimens (Exhibit 4)), US 4,688,517 (automated tissue fixation and embedding (Exhibit 5)), US 3,889,014 (machine for automatic fixation, dehydration, and clearing of tissue specimens (Exhibit 6)). Other examples of automated tissue processing and fixing machines are reported in 3,526,203 (Exhibit 7); 3,771,490 (Exhibit 8); 3,227,130 (Exhibit 9); 2,959,151 (Exhibit 10); 2,386,079 (Exhibit 11); 2,341,198 (Exhibit 12); 2,157,875 (Exhibit 13); 3,400,726 (Exhibit 14); 2,681,298 (Exhibit 15); and 2,684,925 (Exhibit 16). In summary, methods for preparing fixed treated samples from multiple tissues were well known at the priority date of the instant patent Application and automated machines and methods for fixing tissues have been the subject of numerous patents.

Second, the Examiner asserts that the disclosure provides one working example and fails to disclose any other conditions for performing the claimed method. (Office Action, page 7, first paragraph). Applicants traverse and note that Examples are not required in a Specification. See, MPEP §2164, "[c]ompliance with the enablement requirement of 35 U.S.C. [§] 112, first paragraph does not turn on whether an example is disclosed." The instant specification have provided a working Example and sufficient description throughout the text to practice the claimed invention. Specific teachings that may be found in the Specification is detailed below. For example the process of preparing a sample of fixed treated tissue is described in the Specification on page 16 line 7 to page 17 line 17 and on page 23 line 22 to page 25 line 11. The process of preparing cell lines and tissue for FISH is described in the Specification on page 17, line 19 to page 18 line 22. The process of fluorescence in situ hybridization (FISH) is described

in the Specification on page 18 line 24 to page 21 line 14. In addition, the Example section provides description for at least one method for performing the claimed invention. For these reasons, Applicants assert that the instant specification has provided a working Example and sufficient description throughout the text so that one of skill in the art would know how to practice the claimed invention without undue experimentation.

Third, the Examiner assert that the specification does not disclose the composition of the a solution for deparaffinization and antigen retrieval. (Office Action, page 7). Applicants traverse this basis for rejection because solutions for performing deparaffinization and antigen retrieval was well known and commercially available at the time the instant application was filed (i.e., July 21, 2003). For example, it was known at the time the instant application was filed that "Declere™" solution from Cell Marque or "Reveal™" solution from BioCare Medical can both perform deparaffinization and antigen retrieval steps using just one solution. As support, Applicant submit a material data sheet from Sigma-Aldrich which shows that the Declere™ solution was available since at least August 2001 (See, Exhibit 17, date stamp of August 2001 on the bottom right hand corner). Applicants asserts that it is not necessary for the instant Specification to list the formulation of solutions that are well known and commercially available to those of skill in the art.

Fourth, the Examiner asserted that the specification does not provide "an adequate description of any probe, labeled or otherwise" (Office Action, page 7, first paragraph) as a basis for rejection. It is Applicants' position that the description of probes and labels is immaterial to instant pending claims. The claimed methods and compositions, as embodied in pending claims 1-13 and 33 do not encompass probes or labels and do not contain language directed to probes or labels. It is immaterial whether probes and labels are described in the specification because only the claimed invention is required to be supported by the specification. Since the claimed do not recite probes or labels, the basis of rejection is moot.

For the reasons stated above, it is therefore asserted that the instant application has met the requirements for written description for the claimed invention under 35 U.S.C. 112. Withdrawal of this ground of rejection is respectfully requested.

§ 112 First Paragraph - enablement

Claims 1-13 and 33 stand rejected under 35 U.S.C. § 112 first paragraph as allegedly nonenabling. Applicants traverse.

The Examiner listed two basis for rejecting the claims. Each of the Examiner's basis of rejection is discussed below.

First, the Examiner contends that the claims are not enabled because the claims encompasses using virtually any temperature, pressure and duration and that the disclosure fails to provide conditions under which the claimed method can be practiced for the full genus of cells and tissues. As discussed above, the claimed invention is directed to a method of prepared cell lines and tissues and such methods are well known. Furthermore, methods for pressure cooking a sample are well known. For Example, "pressuring cooking" is described in the review article by Shi et al. (Antigen Retrieval Immunohistochemitry: Past, Present, and Future, J. Histochemistry and Cytochemistry 45:327-43 (1997) (Exhibit 18)) and also by Miller et al. (Heat-induced epitope retrieval with a pressure cooker - suggestions for optimal use. Appl. Immunohistochem. 3:190-93 (1995) (Exhibit 19)) and Norton et al. (Brief, High-Temperature Heat Denaturation (Pressure Cooking): A Simple And Effective Method Of Antigen Retrieval For Routinely Processed Tissues., J. Pathol. 173:371-79 (1994) (Exhibit 20)). In addition, solely in an effort to expedite prosecution, Applicants have amended the independent claims to recite the pressure cooking is performed at a temperature of 125°C and a pressure of between 20 to 24 PSI. For these reasons, Applicants assert that a person of skill in the art would know the proper temperature, pressure and other conditions to practice the invention without undue experimentation.

Second, the Examiner alleged that the specification is not enabled because "it fails to set forth a reproducible procedure whereby the resultant product is used to overcome art-recognized

issues of enablement - namely, a problem set forth in Muhlhahn et al. (US 2004/0038270) associated with cells or tissue detaching from a slide while FISH is conducted" (Office Action, page 9, lines 19-24).

Applicants note that Fluorescence In Situ Hybridization (FISH) is an established technique widely accepted in the art as a valid and verifiable approach for clinical diagnosis and research. Numerous researchers and other persons of skill in the art have successfully used FISH in spite of the alleged problems cited by the Examiner. For Example, numerous patents have been issued for methods involving FISH. See, e.g., US 6,548,259 entitled multiparametric fluorescence *in situ* hybridization (Exhibit 21); US 6,506,563 entitled multiparametric fluorescence *in situ* hybridization (Exhibit 22); US 6,221,607 entitled automated fluorescence in situ hybridization detection of genetic abnormalities (Exhibit 23); US 6,136,540 entitled automated fluorescence in situ hybridization detection of genetic abnormalities (Exhibit 24); US 6,043,037 entitled rapid method for measuring clastogenic fingerprints using fluorescence *in situ* hybridization (Exhibit 25); US 6,007,994 entitled multiparametric fluorescence *in situ* hybridization (Exhibit 26); 5,792,610 entitled method for conducting multiparametric fluorescence *in situ* hybridization (Exhibit 27); and US 5,759,781 entitled multiparametric fluorescence *in situ* hybridization (Exhibit 28). Furthermore, fluorescence *in situ* hybridization (FISH) has been used in a variety of areas of research and clinical diagnostics for over 10 years (See, e.g., Gray, J. W. et al., Curr Opin Biotech 3:623-631 (1992) (Exhibit 29); Xing, Y. et al., In: The Causes and Consequences of Chromosomal Aberrations. I. R. Kirsch Ed. CRC Press, Boca Raton, pages 3-28 (1993) (Exhibit 30)).

Based on the numerous reports of successful applications of FISH, Applicants respectfully asserts that ordinary artisan can practice FISH without undue experimentation in spite of the alleged problems "with cells or tissue detaching from a slide while FISH is conducted" (Office Action, page 9, lines 19-24). In view of the detailed description, working example, and well-known techniques and factors disclosed in the instant application, it is respectfully asserted that the application provides sufficient guidance for the claimed methods

and composition. Withdrawal of the rejection of pending claims 1-13 and 33 is respectfully requested.

§ 103

Claims 1-13 and 33 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Engle and Baschong. Applicants traverse.

There is no motivation to combine Baschong with Engel because the two references are directed to incompatible methods.

Engel is directed to inspection of immunostained tissue section by light microscopy at low magnification of 10x or 40x. See, Engel, page 38, col. 1, first paragraph. Because Engel's method uses light microscopy, it does not use an excitation frequency to stimulate fluorescence and it cannot detect autofluorescence (or any fluorescence). For this reason, autofluorescence cannot be a problem in Engel's method. In contrast to Engel, Baschong is directed to controlling autofluorescence in confocal laser scanned tissue. See, Baschong, title. A person of skill in the art would find no reason to combine the autofluorescence technique of Baschong with Engel because autofluorescence is not a problem and is, in fact, undetectable in Engel's low magnification (10x to 40x) light microscopy method.

There Is No Expectation of Success Even If Engel and Baschong Were Combined

There is no expectation of success even if Baschong is combined with Engle. Baschong have conflicting results and states "the result of the present study highlight the fact that there is no general recipe available for the control of autofluorescence. Success was found in a tactical approach that can be summarized as choice of the appropriate reagent(s) by trial and error . . ." Baschong, page 1571, first column. Since Baschong have made no suggestions as to a method for reducing autofluorescence, a combination of Baschong and Engle, is merely an experiment which, in Baschong's characterization, involves choosing the appropriate reagents by trial and

error. Further, as discussed in the next section, a combination of Baschong and Engel in any event would not lead to Applicants' claimed invention.

Even If Baschong And Engle Were Combined, It Would Not Lead To Applicants' Claimed Methods And Compositions

The claimed invention, is directed to a method used for preparing cell-line and/or tissue samples. In the method, cells are pressured cooked and treated with ammonia-ethanol and sodium borohydride (See, e.g., claims 1 and 33). Other claims are directed to compositions comprising a fixed-treated tissue, ammonia-ethanol and sodium borohydride.

Baschong teaches that a combination of ammonia-ethanol treatment and sodium borohydride treatment is undesirable by stating:

> "[t]o our surprise, treatment with borohydride induced bright autofluorescence in erythrocytes that had otherwise remained inconspicuous (Figure 1F). **This undesirable effect** was slightly diminished by adding ammonia-ethanol (Figure 1G) or sudan [black B] (Figure 1H) and even better if both reagents were combined (Figure 1I). Nevertheless, borohydride treatment once applied, autofluorescence in erythrocytes could not be completely abolished (Figure 1I)." Baschong at page 1567 (emphasis added).

As discussed above, Engel refers to wet heat treatment for paraffin wax embedded tissues and is silent on the suppression of autofluorescence. One of skill in the art, in reading Baschong and Engle, would be discouraged from using a combination of borohydride and ammonia ethanol because Baschong states that the undesirable autofluorescent effect of borohydride treatment "could not be completely abolished."

In fact, the cited references teaches away from the claimed invention. In contrast to the undesirable effects of borohydride and ammonia ethanol, Baschong states "A near to total absence of autofluorescence was attained by treatment with ammonia-ethanol and Sudan [black B]." Baschong at page 1567. Thus, there is no motivation to combine Baschong with Engel to

come up with Applicant's claimed invention. At best, a combination of Baschong and Engel would lead to the use of ammonia-ethanol and Sudan black B which does not contain all the recitations of Applicants' claims.

For the reasons stated above, Applicants believe that the rejection of claims 1-13 and 33 under 35 U.S.C. § 103 was improper and should be withdrawn in view of Applicants arguments.

CONCLUSION

Applicants have corrected "Amended Claim" 33 to reflect "New" Claim 33 to comply with the Notice of Non-Compliant Amendment (37 CFR 1.121). No new matter has been added and the entry of the amendments are respectfully requested.

On the basis of the foregoing amendment and remarks, Applicants respectfully submit, that the pending claims are in condition for allowance. If there are any questions regarding this amendment and remark, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

While Applicants believe that no additional fees are due, the Director is authorized to charge all fees that may be due, or to credit any overpayment, to the undersigned's account, Deposit Account No. **50-0311**, Ref. No. **24817-503**, Customer No. **35437**.

Respectfully submitted,

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